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Tolerance to bronchodilating effects of salmeterol in COPD

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Summary Loss of bronchodilator effectiveness or tolerance has been observed with inhaled beta-agonists but not with inhaled anticholinergic medications. Initially, tolerance is reflected in loss of bronchial protection against stimuli followed by loss of bronchodilator properties. However, generally such observations have been reported in asthma. A 6-month randomized, double-dummy placebo-controlled trial comparing tiotropium to salmeterol provided the opportunity to examine spirometric tolerance to long-acting beta-agonists in patients with COPD. Spirometry was measured over 12 h at baseline and at days 15, 57, 116 and 169. Changes over time from baseline were compared relative to changes observed with placebo. A total of 623 patients participated (tiotropium = 209, salmeterol = 213, placebo = 201). The groups were similar in age (mean = 65 years), gender (75% men), and baseline FEV_1 (mean = 1.08 ± 0.37 l [40 ± 12% predicted]). Relative to placebo, both active drugs improved morning pre-drug, peak and average FEV_1 and FVC throughout the trial. However, from day 1 to 169, salmeterol was associated with a higher decline in average FEV_1 and FVC (0–12 h) (difference from placebo: −36 and −115 ml, $P<0.05$), which was most prominent over the 8–12 h period (difference from placebo: −45 and −138 ml, $P<0.01$). Significant declines in peak FVC relative to placebo (−83 ml, $P<0.05$) but not FEV_1 (−12 ml) were observed with salmeterol. Tiotropium was associated with further improvements in spirometry from days 1 to 15 and no evidence of tolerance from day 15 to the end of the trial. In conclusion, tolerance to pharmacologic bronchodilation occurs with long-acting beta-agonists such as salmeterol and not with inhaled anticholinergics.

Introduction

Treatment for COPD involves a step-wise approach of adding more bronchodilators over time as the disease progresses.[1,2] Therapeutic algorithms have identified the benefits of regularly scheduled inhaled bronchodilators in the treatment of COPD. Inhaled medication has been recognized as the preferred route due to the topical delivery and favorable efficacy to side-effect profile. Several classes of bronchodilators exist and are defined by their mechanism of action; differences within a class are distinguished with regard to dosing frequency (e.g. short- vs. long-acting bronchodilators). In addition to the differences in side-effect profiles between classes of inhaled bronchodilators, there may also be pharmacological differences with regard to efficacy over time. Specifically, inhaled beta-agonists have been associated with tolerance to their bronchoprotective effects in asthma.[3–5] There is additional information that bronchodilator subsensitivity to short-

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acting inhaled beta-agonists occurs following chronic treatment with long-acting beta-agonists.[6–8] Such phenomenon corresponds to in vitro data indicating subsensitization at a receptor level.[8,9]

While clinical evidence of tolerance has occurred in asthma and is generally well accepted, tolerance to chronic administration of inhaled beta-agonists has not been adequately addressed in patients with COPD. Documentation and investigations evaluating tolerance to bronchodilators in COPD may be useful for clinicians who wish to incorporate this knowledge into prescribing practices. The completion of a large 6-month clinical trial (previously reported by Donohue et al.)[10] evaluating the effects of tiotropium, salmeterol and placebo in patients in COPD has allowed for the opportunity to evaluate differences in maintenance or tolerance to pharmacologic bronchodilation between these two major classes of medications. We, therefore, wish to report the results of a retrospective analysis of serial spirometric testing over 12 h in approximately 600 patients with COPD during a 6-month treatment period.

Methods

Study design

A multicenter, multinational, randomized, parallel-group study of 6-month duration was performed to compare the long-term efficacy of tiotropium dry powder inhalation capsules with salmeterol inhalation aerosol and placebo in patients with COPD. A double-dummy design was incorporated where all patients received one capsule (tiotropium or placebo) through the HandiHaler® device once daily and two actuations (salmeterol or placebo) from a metered dose inhaler twice daily. Tiotropium dosing was 18 μg once daily and salmeterol dosing was 50 μg twice daily.

Patients

Patients were required to have a physician diagnosis of COPD and relatively stable obstructive airways disease with a forced expiratory volume in 1 s (FEV_1) $\leqslant$60% of predicted normal and FEV_1 $\leqslant$70% of forced vital capacity (FVC).[11] Inclusion criteria also required patients to be at least 40 years of age and have a smoking history exceeding 10 pack-years. Exclusion criteria included a history of asthma, allergic rhinitis or atopy, an elevated eosinophil count, recent respiratory tract infection, regular daytime supplemental oxygen for more than 1 h per day and a significant disease other than COPD. A significant disease was defined as a disease that in the opinion of the investigator would put the patient at risk because of participation in the study or a disease which would influence the results of the study. The protocol was approved by Institutional Review Boards and written, informed consent was obtained before any study procedure was undertaken.

Study protocol

A 2-week baseline period preceded randomization. Clinic visits were held at –2 weeks, 0 weeks (randomization) and at 2, 8, 16 and 24 weeks. 12-h spirometry was performed at each visit following successful completion of the baseline period. Spirometry was conducted prior to the start of therapy at –60 and –10 min pre-dose at the randomization visit and at 30, 60 min, 2, 3, 4, 6, 8, 10 and 12 h post-dosing using the Ko–Ko® spirometer (Pulmonary Data Services, Louisville, CO, USA). Measurements were performed according to American Thoracic Society criteria.[12] The highest values of FEV_1 and FVC measurements were retained. Short-acting theophyllines were withheld at least 24 h, long-acting theophyllines at least 48 h and short-acting β_2-agonists 8 h before spirometry. Patients were allowed to continue previously prescribed regular inhaled steroids or regular oral steroids not exceeding a dose equivalent to approximately 10 mg prednisone daily.

Data analysis

Analysis of covariance was performed with the baseline being used as a covariate. Baseline FEV_1 was defined as the mean of the FEV_1 recordings 60 and 10 min prior to the first dose of study medication. A similar calculation was performed on all other study days; however, the calculated value on these days will be referred to as the trough FEV_1 (i.e., FEV_1 approximately 23–24 h after the previous dose of tiotropium or 11–12 h after the previous dose of salmeterol). All randomized patients with data at baseline and following 2 weeks of treatments were included in analysis. For the patients who discontinued due to worsening (3.3% in tiotropium, 10.3% in salmeterol, and 14.9% in placebo) the least favorable data were carried forward to impute the missing data. For all other patients their missing data (9.3%) were imputed by

their last observation. In order to be able to include the same patients at each time point in the spirometry summaries, missing values were estimated using other values recorded for the patient on that test day. Linear interpolation between the two adjacent measurements was used to estimate missing spirometry values from the middle of the profile. For values at the end of the profiles that were missing because rescue medication was taken, the minimum observed FEV_1 value on that test day was used as the estimate. The last available value was used as the estimate for data that were missing for administrative reasons unrelated to the patient's response to treatment. Unless otherwise specified, data are presented as means ± standard deviation. Statistical significance was considered at $P < 0.05$.

Results

Demographics

Six-hundred and twenty three patients were randomized. Two-hundred and nine patients received tiotropium, 213 received salmeterol and 201 received placebo. There were no significant differences in baseline demographics among the three treatment groups (Table 1). The mean age of the population was 65 ± 8 years, with 75% being men. Mean FEV_1 was 1.08 ± 0.37 l (40.2 ± 12.1% predicted). There were no significant differences among the groups according the baseline respiratory medication use. Approximately 66% of patients reported taking regular inhaled steroids. The mean FEV_1 for each treatment group at screening was: tiotropium 1.11 ± 0.39 l (41% predicted), salmeterol 1.07 ± 0.37 l (39% predicted) and placebo 1.06 ± 0.36 l (41% predicted).

Improvements from baseline

Both active treatments resulted in significant improvements in trough, peak and average (0–12 h) FEV_1 and FVC compared to placebo; these results have been reported elsewhere. On day 1 (first dose), the improvements with both active treatments were similar. At the end of the trial the improvements in trough, peak and average values were superior with tiotropium vs. salmeterol. The aforementioned results have been reported elsewhere.[10]

Tolerance

Tolerance was measured as the decline in response after treatment was initiated. As the trough response could not be observed until day 15, the change in trough response was defined as the change from day 15 to the end of treatment. For the peak and average values, the change in response was defined as the change from day 1 to the end of treatment. As there appeared to be increasing improvements with tiotropium from days 1 to 15, the change in peak and average response was also evaluated for the change from day 15 to the end of treatment.

The changes in the magnitude of responses for FEV_1 and FVC from days 1 to 169 are recorded in Table 2; the changes from days 15 to 169 are recorded in Table 3. From days 1 to 169, salmeterol was associated with a higher decline in average FEV_1 and FVC (0–12 h) (difference from placebo: −36 and −115 ml, $P < 0.05$) which was most prominent over the 8–12 h period (−95 and −138 ml for FEV_1 and FVC, $P < 0.01$). Significant declines in peak FVC relative to placebo (−83 ml, $P < 0.05$) but not FEV_1 (−12 ml) were also observed with salmeterol. Tiotropium was associated with further improvements in spirometry from days 1 to 15 and no evidence of tolerance from day 15 to the end of the trial.

Table 1 Baseline demographics and patient characteristics for the tiotropium ($n = 209$), salmeterol ($n = 213$) and placebo ($n = 201$) groups.

	Tiotropium	Salmeterol	Placebo
Age (years)*	64.5 ± 7.9	64.6 ± 8.1	65.6 ± 7.8
Male (%)	74	75	75
Duration of COPD (years)*	9.2 ± 7.8	10.4 ± 8.2	9.7 ± 7.9
Smoking (pack years)*	47 ± 25	48 ± 26	46 ± 24
FEV_1 (l)*	1.11 ± 0.39	1.07 ± 0.37	1.06 ± 0.36
FVC (l)*	2.54 ± 0.71	2.57 ± 0.76	2.58 ± 0.74
FEV_1/FVC*	43.6 ± 9.8	42.0 ± 9.5	41.3 ± 8.7

*Mean ± SD.

Table 2 Mean [SE] FEV_1 response following 24 weeks treatment. *P*-values indicate statistical significance in comparison to placebo.

	Tiotropium	Placebo	Salmeterol
Trough response (ml):			
Day 169–15	−13 [13]	−14 [13]	−35 [13]
Peak response (ml):			
Day 169–1	20 [15]**	−44 [16]	−56 [15]
Day 169–15	−21 [13]	−26 [14]	−26 [13]
Average 0–4 h (ml):			
Day 169–1	22 [14]*	−32 [15]	−50 [14]
Day 169–15	−21 [12]	−13 [13]	−25 [12]
Average 4–8 h (ml):			
Day 169–1	−1 [14]	−25 [15]	−68 [14]*
Day 169–15	−12 [13]	−12 [13]	−23 [13]
Average 8–12 h (ml):			
Day 169–1	−3 [13]	−21 [14]	−66 [13]*
Day 169–15	−8 [13]	−10 [13]	−27 [13]
Average 0–12 h (ml):			
Day 169–1	5 [13]	−25 [14]	−61 [13]*
Day 169–15	−13 [12]	−11 [13]	−25 [12]

*$P < 0.05$, **$P < 0.01$.

Table 3 Mean [SE] FVC response following 24 weeks treatment. *P*-values indicate statistical significance in comparison to placebo.

	Tiotropium	Placebo	Salmeterol
Trough response (ml):			
Day 169–15	−19 [25]	−16 [26]	−70 [25]
Peak Response (ml):			
Day 169–1	−24 [28]	−60 [30]	−143 [28]*
Day 169–15	−69 [26]	−70 [26]	−60 [27]
Average 0–4 h (ml):			
Day 169–1	−7 [25]	−40 [27]	−115 [25]*
Day 169–15	−64 [23]	−37 [25]	−65 [23]
Average 4–8 h (ml):			
Day 169–1	−56 [26]	−34 [28]	−161 [26]**
Day 169–15	−49 [24]	−31 [25]	−76 [24]
Average 8–12 h (ml):			
Day 169–1	−35 [25]	−17 [27]	−155 [25]**
Day 169–15	−19 [23]	−13 [25]	−84 [23]*
Average 0–12 h (ml):			
Day 169–1	−31 [24]	−27 [25]	−142 [24]**
Day 169–15	−41 [22]	−23 [23]	−75 [22]

*$P < 0.05$, **$P < 0.01$.

Discussion

A full appreciation of the pharmacologic profile of therapeutic interventions can assist prescribers in treating patients with COPD. All classes of bronchodilators have been shown to improve FEV_1 in the treatment of COPD, although there may be differences to the degree of improvement. One of the properties not well documented is that of maintenance of bronchodilation and tolerance to bronchodilation over time. The present clinical study illustrates that tolerance to bronchodilation seen with inhaled medications differs between classes. Specifically, the long acting beta-agonist salmeterol was associated with diminishment of bronchodilating effects which

was most prominent towards the end of the dosing interval. The majority of tolerance occurred within a few weeks. However, there seemed to be continued diminishment of bronchodilating effects to salmeterol over the 6 months of the study.

The majority of information regarding tolerance has come from studies in asthma. Early studies of isolated human peripheral airways smooth muscle undergoing stimulation showed concentration-dependent tachyphylaxis to isoprenaline.[13] In addition, there is subsensitization to beta$_2$-receptors in vitro.[8,9] Clinical data support the in vitro studies. O'Connor et al. observed that 7 days treatment with a short-acting beta-agonist (terbutaline) reduced the protection against methacholine-induced bronchoconstriction and eliminated the protection against AMP in patients with asthma.[3] Cockcroft et al. noted reduced protection against an allergen challenge following chronic dosing with albuterol.[5] Similar attenuation of bronchoprotection has also been observed with salmeterol administered to patients with asthma.[4] Simons et al. documented tolerance to the bronchoprotective effect of salmeterol to an exercise stimulus in asthma has also been documented.[14] Of note, the bronchoprotective effect waned towards the end of the dosing interval but not at 1 h. The present investigation documented that the most prominent evidence of tolerance also occurred toward the end of the dosing interval.

Investigators have examined whether inhaled steroids may counteract the tolerance that has been observed with inhaled beta-agonists with asthma. In vitro data suggest that desensitization can be at least partially reversed by corticosteroids.[15,16] However, clinical studies indicate that inhaled steroids do not protect against tolerance.[14,17] Our data is consistent with such reports in that tolerance to salmeterol in patients with COPD occurred despite 2/3 of the population receiving inhaled corticosteroids although the doses varied and were not standardized within the population.

The maintenance of acute responses to short-acting inhaled beta-agonists has been evaluated following chronic treatment with long-acting beta-agonists. Both salmeterol and formoterol induce significant bronchodilator subsensitivity to repeated doses of albuterol in some studies but not in others.[6,7,18,19] In a study of 12 patients with asthma, the subsensitivity could be partially reversed by a large single dose of intravenous or inhaled corticosteroid.[7] Overall the body of evidence favors tolerance to beta-agonists occurring with chronic administration in asthma. There is sparse information as to whether there are unfavorable effects of chronic administration of beta-agonists in patients with COPD. In a 2-year study of patients with moderate asthma or chronic bronchitis, regular administration of bronchodilators was associated with an increase in the rate of decline in lung function compared to as-needed use.[20] However, these results have not been confirmed.

It is possible that due to the different pathogenic mechanisms involved in bronchoconstriction in COPD compared to asthma, that tolerance to beta-agonists may not occur or that the magnitude of tolerance may be different. Controlled clinical studies in patients with COPD examining up to 4 months treatment with formoterol or salmeterol have suggested that tolerance does not appear to occur although specific analyses addressing the issue were not reported.[21,22] Laboratory-based testing of protection against induced bronchoconstriction in COPD have not been reported but may not be an appropriate evaluation for tolerance in patients with COPD.

Although diminishment of the bronchodilation observed with salmeterol was observed by day 15, the changes appeared to progress with time, i.e. there was further loss of the bronchodilator effect from days 113 to 169. The clinical results are inconsistent with in vitro observations that tolerance occurs rapidly. The explanation for the observation remains unclear. However, the magnitude of the diminishing bronchodilator effect of salmeterol was relatively small; several of the variables analyzed were not statistically significant. It is likely that these small decrements in lung function over time would not be detected clinically by patients other than under unusual circumstances.

The present study indicated that diminishment of FEV_1 and FVC responses, particularly at the end of the dosing interval (i.e. 8–12 h post-dose) does occur in COPD patients treated with salmeterol. It is unclear as to why tolerance was exhibited in this study and not in previously published COPD clinical trials with salmeterol or formoterol. Several possibilities exist. First, the population under study could be different. While in all studies, there are slight nuances to the inclusion and exclusion criteria generally all have attempted in a reasonable fashion to include stable COPD with documented airflow limitation and exclude asthma. Second, there may be differences in the degree of tolerance based on responsiveness to acute administration of a short-acting agent. There is variability in the magnitude of response

of beta-agonists on a given day between patients. Although in some studies, a sub-analysis has been performed based on initial acute bronchodilator response to an inhaled short-acting beta-agonists (albeit not with regard to tolerance), generally, the studies have not excluded patients on their basis of magnitude of response. This hypothesis cannot be evaluated as an assessment of acute bronchodilation following inhalation of a short-acting beta-agonist was not performed in this study. Third, the analysis plan may have differed among the studies. None of the previous studies had specifically targeted declines in response at the end of dosing period as in the present analysis. Fourth, the duration of the study may have influenced the ability to discern tolerance. Although, on a cellular level, tolerance occurs within a week and can occur clinically within 24 h, we have observed that progressive changes do appear to occur over longer periods of time. The other studies were of shorter duration, but this is likely an inadequate explanation. Fifth, none of the studies, including the present study specifically set out to evaluate tolerance as the primary outcome. Hence, ideally a study designed that targets pharmacologic tolerance would be of interest.

In summary, albeit relatively small, diminishment of bronchodilator responses and duration of bronchodilation over time was observed in patients with COPD during chronic administration of salmeterol 50 μg bid delivered by a metered dose inhaler but not with tiotropium 18 μg b.i.d. delivered by the HandiHaler®. Although most of the observed tolerance with salmeterol appeared within a few weeks of chronic administration, further evidence of diminished effectiveness was observed over months of treatment. While tolerance in a COPD clinical trial has not previously been reported, the reasons for this observation being different from other reported trials remains speculative. Given the discrepant information, the data presented should be confirmed in a prospective trial designed specifically to examine for tolerance. Additional information may also be gleaned through trials evaluating bronchoprotective effects of chronic treatment with inhaled beta-agonists in patients with COPD. Nevertheless, the concept of tolerance may need to be considered when re-evaluating COPD patients during chronic treatment with long-acting beta-agonists.

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